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/Janet A. Sherrill/ November 16, 2011
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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants	:	Stanton L. Gerson
Serial No.	:	09/321,655
Filing Date	:	May 28, 1999
For	:	HEMATOPOIETIC PROGENITOR CELL GENE TRANSDUCTION
Confirmation No.	:	6848
Group Art Unit	:	1633
Examiner	:	Quang Nguyen
Attorney Docket No.	:	CWR-7091 NP

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

APPEAL BRIEF

Sir:

Pursuant to the Notice of Appeal filed with respect to the above-identified application, Appellants present herewith their Brief on Appeal.

I. REAL PARTY IN INTEREST

The real parties in interest is, Case Western Reserve University as indicated by the assignment recorded Reel No: 010274/Frame: 0886.

II. RELATED APPEAL AND INTERFERENCES

There are no related appeals, interferences, or judicial procedures under 37 C.F.R. §41.37(1)(c)(ii).

III. STATUS OF CLAIMS

Claims 1and 6 are cancelled.

Claims 2, 3-5 and 7 are finally rejected and hereby appealed.

IV. STATUS OF AMENDMENTS

An amendment amending claim 7 to overcome a claim objection per the Examiner's suggestion has been filed concurrently herewith.

V. SUMMARY OF THE CLAIMED SUBJECT MATTER

A first aspect of the present invention, which is recited in claim 5, is directed to a method for transforming hematopoietic progenitor cells to express a protein (Page 4, lines 8-10 and page 7, lines 10-12). The method includes co-culturing human hematopoietic progenitor cells with a homogenous population of human mesenchymal stem cells that have been isolated, purified and then culturally expanded from human mesoderm tissue (page 4, lines 8-10, page 5, lines 24-25, page 9 lines 25-30 and page 10, lines 1-10). The method also includes transforming the human hematopoietic progenitor cells with a polynucleotide (Page 7, lines 7-12). The polynucleotide includes exogenous genetic material encoding a protein in the

presence of the isolated, purified, and culturally expanded human mesenchymal stem cells (Page 7, lines 7-12, page 9 lines 25-30, and page 10, lines 1-10).

Claim 2 depends from claim 5 and recites that the mesenchymal cells are autologous to the hematopoietic progenitor cells (Page 4, lines 12-13).

Claim 3 depends from claim 5 and recites that the mesenchymal stem cells are allogeneic to the hematopoietic progenitor cells (Page 4, lines 13-14).

Claim 4 depends from claim 5 and further recites the step of separating the transformed human progenitor cells from the mesenchymal stem cells (Page 6, lines 17-22).

Claim 7 depends from claim 5 and recites the homogenous population of mesenchymal stem cells uniformly expressing SH2, SH3, and SH4 surface antigens, and lacking surface markers for T and B lymphocytes, macrophages, and endothelial cells (page 5, lines 14-17, and page 10, lines 1-5).

VI. GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

A. Whether claims 3-5 are anticipated under 35 U.S.C. §102(b) by Nolta *et al.* (Blood 86:101-110, 1995) (hereinafter, "Nolta et al") as evidenced by Prockop, D.J. (Science 276:71-74, 1997) (hereinafter, "Prockop") and/or U.S. Patent Application No. US2002/0168765 to Prockop et al. (hereinafter, "the '765 Application").

B. Whether claims 2 and 4-5 are anticipated under 35 U.S.C. §102(b) by Wells *et al.* (Gene Therapy 2:512-520, 1995) (hereinafter, "Wells et al") as evidenced by Prockop and/or the '765 publication.

C. Whether claims 5 and 7 are obvious under 35 U.S.C. §103(a) in view of either Nolta et al. or Wells et al. and Prockop and U.S. Patent No. 5,486,359 to Caplan et al. (hereinafter, "Caplan et al.").

VII. ARGUMENTS FOR CLAIMS 3-5

Claims 3-5 were rejected under 35 U.S.C. §102(b) as being anticipated by Nolta et al. as evidenced by Prockop and/or the '765 Application.

The most recent Office Action, mailed November 16, 2010 argues that, Nolta *et al.* disclose a transduction method for human CD34 cells isolated from bone marrow and peripheral blood with retroviral vectors containing either the bacterial neo gene, or normal human glucocerebrosidase in the presence of stroma generated by 4th passaged human allogeneic bone marrow stromal cells prior to the plating of CD34 cells. The Office Action also argues that the utilized bone marrow stromal cell population derived from bone marrow spicules is devoid of most hematopoietic cells except for mature macrophages which comprised less than 1% of the culture, and it contains isolated mesenchymal stem cells or isolated multipotential bone marrow stromal cells (MSCs) as evidenced by the teaching of Prockop (Science, abstract and p 73, col. 3), including the disclosure that the adherent cells used as feeder layers for hematopoietic stem cells have many of the characteristics of MSCs isolated by their adherence to plastic in the absence of non-adherent cells. The Office Action further argues that the terms "Mesenchymal stem cell" and "Marrow stromal cell" have been used interchangeably in the art as evidenced at least by the teachings of the '765 publication which states: "Bone marrow contains at least two kinds of stems cells, hematopoietic stem cells and stem cells for non-hematopoietic

tissues variously referred to as mesenchymal stem cells or marrow stromal cells (MSCs)"; and "Marrow stromal cells (MSCs) are adult stem cells from bone marrow that can differentiate into multiple non-hematopoietic cell lineages".

The Examiner concludes that the bone marrow stromal cells that were passaged four times for transduction as taught by Nolta *et al* were mesenchymal stem cells that have been isolated, purified and culturally expanded from human mesoderm tissue. Further, the Examiner states that the utilized cell population can be considered to be homogeneous because it is devoid of most hematopoietic cells expect for mature macrophages which comprised less than 1% of the culture.

Applicants respectfully submit that claim 5 is not anticipated by Nolta *et al*. as evidenced by Prockop and/or the '765 publication, because Nolta *et al*. do not teach a homogenous population of mesenchymal stem cells that have been isolated, purified, and then culturally expanded, as claimed in the present application. Specifically, Applicants note that Nolta et al. do not teach a homogenous population of human mesenchymal cells that have been isolated, purified, and then culturally expanded from human mesoderm tissue and the claimed isolated, purified and then culturally expanded homogenous population of mesenchymal stem cells are not identical to the stromal cells of Nolta *et al*.

In order for a claim to be anticipated each and every element of the claimed invention, operating in the same fashion to form the identical function as the claimed product must be literally present in a single prior art reference, arranged as in the claim. *Scripps Clinic & Research Found. v. Genentech, Inc.* 927 F.2d 1565, 1576 (Fed. Cir. 1991); Carella v. Starlight Archery & Pro Line Co., 804 F.2d at 138. "There

must be no difference between the claimed invention and the referenced disclosure, as viewed by a person of ordinary skill in the field of the invention." *Scripps Clinic & Research Found. v. Genentech, Inc., 927 F.2d at 1576; see also E.I. Du Pont de Nemours & Co. v. Polaroid Graphics Imaging. Inc.,* 706 F. Supp. 1135, 1142 (D. Del.1989), (aff'd, 887 F.2d 1095 (Fed. Cir. 1989) ("all of the same elements [must be] found in exactly the same situation and united in the same way ... in a single prior art reference") (quoting *Perkin Elmer Corp. v. Computervision, Corp.,* 732 *F.2d* 888, 894 *(Fed. Cir. 1984)).* It is not sufficient that each element be found somewhere in the reference, the elements must be "arranged as in the claim." *Lindemann Maschinenfabrik GmbH v. American Hoist & Derrick Co.,* 730 F.2d 1452, 1458 (Fed. Cir. 1984). Thus, any degree of physical difference between the patented product and the prior art, *no matter how slight,* defeats the claim of anticipation. *E.I. Du Pont de Nemours & Co. v. Polaroid Graphics Imaging, Inc.,* 706 F. Supp. at 1142.

Nolta *et al*. teaches that,

> "spicules from unseparated bone marrow were collected by gravity sedimentation and plated in stromal medium… [and then] subconfluent layers of primary stromal cells were split by trypsinization. Stroma was not used as a supporting layer for transduction until passage no. 4. At [that] point, most hematopoietic cells had been eradicated, except for mature macrophages, which comprised less than 1% of the culture, as shown by fluorescence-activated cell sorter (FACS) analysis and immunohistochemical staining for the panleukocyte antigen CD45 using the monoclonal antibody HLE-1 as described. Stromal cells were irradiated (20Gy) and plated at 5 x 10^5 cells per T25 vent-cap flask in IMDM/20% FCS the day before use." (p102, col 1, 2^{nd} full para.).

The result of the isolation technique taught by Nolta et al. is a heterogeneous, poorly defined population of marrow derived cells. There is nothing in Nolta et al. that states that this population is a homogenous population of mesenchymal stem cells, let alone a population of mesenchymal stem cells that have been isolated, purified, and then culturally expanded. The mere fact that Nolta et al. teach that stromal cells have been passaged a number of times only suggests that an isolated heterogeneous population has been isolated. There is nothing in Nolta et al. that teaches this isolated population is homogenous and/or is subsequently culturally expanded.

In contrast, claim 5 recites a homogenous population of mesenchymal stem cells that have been isolated, purified, and then culturally expanded. The specification of the application which is used to construe this language teaches at p. 5, ll. 1-12 that:

> [m]esenchymal stem cells (MSCs) can be derived from marrow, periosteum, dermis and other tissues of mesodermal origin. The mesenchymal stem cells can be isolated and prepared according to methods known in the art, for example, a process for isolating, purifying, and expanding the marrow-derived mesenchymal stem cells in culture, i.e. in vitro, is described in U.S. Patent Nos. 5,197,985 and 5,226,914 and PCT Publication No. WO 92/22584 (1992) as well as numerous literature references by Caplan and Haynesworth. The stem cells may be isolated from other cells by density gradient fractionation, such as by Percoll gradient fractionation. The human mesenchymal stem cells also can include a cell surface epitope specifically bound by antibodies from hybridoma cell line SH2, deposited with the ATCC under accession number HB10743l antibodies form hybridoma cell line SH3, deposited with ATCC under accession number HB10744; or antibodies from hybridoma cell line SH4, deposited with the ATCC under accession number HB10745 (Emphasis added).

Appellants note that the mesenchymal stem cells taught in the present application are a specific cell type, possessing defined characteristics recognized by

those skilled in the art, as evidenced by Majumdar *et al.* (J. Cell. Phys. 178:57-66,1998). Majumdar *et al.* discuss the differences between isolated, purified mesenchymal stem cells (MSCs) and marrow-derived stromal cells (MDSCs) (see Abstract). Majumdar *et al.* teach that MSCs are morphologically distinct from MDSC cultures, and flow cytometric analyses show that MSCs are a homogeneous cell population (*Id.*; Figs. 1 & 2). In addition, MSCs were found to have greater steady state levels of cytokine expression than MDSCs (*See* Abstract and Fig. 3). Majumdar *et al.* disclose a method for isolating, purifying and culturally expanding MSCs that utilizes Percoll density centrifugation as a purification step (p58, first full para.). The use of Percoll purification is discussed in the present specification at p. 5, ll. 6-7 and p. 9, ll. 29-30.

Appellants further note that the present application differentiates between MSCs and Dexter stroma. Dexter stroma as discussed in the present specification is equivalent to the MDSCs discussed by Majumdar *et al.* (See Majumdar *et al.* p58, para. spanning col. 1-2 and Experimental Example p10, ll. 13-23.). Thus, one skilled in the art at the time of the invention would have recognized that the MSCs recited in claim 5 are a distinct cell population compared to the heterogeneous stromal cells of Nolta *et al.*

In addition, while there are several art-recognized methods for arriving at a homogenous population of mesenchymal stem cells that have been isolated, purified, and culturally expanded, the present application provides examples of specific methods for arriving at a homogenous population of mesenchymal stem cells that have been isolated, purified, and culturally expanded. Conversely, the

present application does not provide examples of methods for arriving at the heterogeneous, poorly defined population of marrow derived cells of Nolta et al.

The Examiner appears to assert (see Office Action, mailed November 16, 2010 at pg. 6, lines14-16) that because the claim language does not specify a method of isolation, purification, and culture expansion, the methods of Nolta et al. are covered by the scope of claim 5. However, the Examiner must construe the claims in accordance with defined terms in the specification. While it is true that a specific method is not claimed, the specification does teach that MSCs are a distinct population from the more heterogeneous cell population of the marrow stroma (p. 5, ll. 14-17).

Nolta et al. employ an isolation technique based on adherence of stromal cells to plastic cell culture plates. The only isolation and purification is the removal of non-adherent cells by washing the plates. Nolta *et al.* do not characterize or demonstrate that the passaged adherent cells are a homogeneous population of mesenchymal stem cells or that there is even a high proportion of mesenchymal stem cells compared to other cell types. In fact, Nolta *et al.* fails to discuss mesenchymal stem cells at all. Therefore, the isolated cell population taught by Nolta et al. is not identical to the homogeneous cell population of mesenchymal stem cells that have been isolated, purified, and culture expanded as presently claimed.

Moreover, there is nothing in Nolta et al. that teaches the passaged stromal cells of Nolta et al. would inherently be a homogenous population of mesenchymal stem cells. The Examiner infers that mesenchymal stem cells of Nolta et al. are isolated, purified, and expanded by referencing Prockop as support for the presence

of mesenchymal stem cells in the adherent cell population. However, Prockop does not support the argument that mesenchymal stem cells have been isolated, purified, and expanded. Contrary to the position taken by the Examiner, Prockop teaches that there are advantages to utilizing isolation and purification methods as opposed to the "crude procedure of Friedenstein," *i.e.,* the isolation of marrow stromal cells via adherence to plastic alone that is also used by Nolta *et al.* (see p72, col. 1, para. 3 and col. 2, para. 2). These advantages include that "the isolated cells are either clonal or nearly clonal, they express small amounts of bone cell markers such as alkaline phosphatase, and they can be induced in culture to express large amounts of the same markers…" (p 72, col. 2, para 2).

In addition, the most recent Office Action argues that the terms "Mesenchymal stem cell" and "Marrow stromal cell" have been used interchangeably in the art as evidenced by the '765 Publication. Appellants fail to see the relevancy of this argument and respectfully submit that a person of skill in the relevant art would clearly recognize that a homogenous population of mesenchymal stem cells that have been isolated, purified, and then culturally expanded are distinct from the marrow stromal cells taught by Nolta *et al.* Simply because the '765 Publication referred to a single cell type interchangeably as mesenchymal stem cells and marrow stromal cells, the '765 publication does not illustrate that the marrow stromal cells taught by Nolta et al. are identical to the MSCs recited in claim 5.

As discussed above, Majumdar *et al.* discuss the differences between isolated, purified mesenchymal stem cells (MSCs) and marrow-derived stromal cells (MDSCs) (see Abstract). Majumdar *et al.* teach that MSCs are morphologically

distinct from MDSC cultures, and flow cytometric analyses show that MSCs are a homogeneous cell population (*Id.*; Figs. 1 & 2). In addition, MSCs were found to have greater steady state levels of cytokine expression than MDSCs (*See* Abstract and Fig. 3). Majumdar *et al.* disclose a method for isolating, purifying and culturally expanding MSCs that utilizes Percol density centrifugation as a purification step (p58, first full para.). The use of Percol purification is discussed in the present specification at p. 5, ll. 6-7 and p. 9, ll. 29-30.

Appellants note that the present application differentiates between MSCs and Dexter stroma. Appellants further note that Dexter stroma as discussed in the present specification is the same as the MDSCs discussed by Majumdar *et al.* (See Majumdar *et al.* p58, para. spanning col. 1-2 and Experimental Example p10, ll. 13-23.). Thus, one skilled in the art would recognize that the MSCs recited in claim 5 are a distinct cell population from the heterogeneous stromal cells discussed by Nolta *et al.*

The most recent Office Action notes that the instant specification states "These results demonstrate that hMSCs are able to support ex vivo gene transfer into CD34 human hematopoietic progenitor cells that exhibit transduction efficiencies, cell expansion and drug resistance comparable to the levels produced in Dexter Stroma and FN enhanced transduction", and that "Dexter Stroma was derived from adhered bone marrow mononuclear cells that were passaged once". The statements cited by the Examiner were not intended to, nor do they illustrate that the cell populations of Dexter Stroma and the MSCs isolated from human mesoderm tissue are substantially identical cell populations. This statement was merely

included in the present Application to illustrate the effectiveness of the present invention in relation to other methods of *ex vivo* gene transfer into human hematopoietic progenitor cells known at the time of the present invention.

The Examiner argues in response to Appellants' previous argument put forth that the stromal cell population is devoid of most hematopoietic cells and contains MSCs as evidenced by Prockop (pg. 6, lines 17-21, of the most recent Office Action, mailed November 16, 2010) and that this bone marrow derived stromal cell population have many of the characteristics of MSCs (pg. 3, lines 20-22 of the most recent Office Action, mailed November 16, 2010).

However, a heterogeneous bone marrow stromal cell population is not identical to a homogenous population of mesenchymal stem cells isolated, purified and then culturally expanded from human mesoderm tissue even if it shares many characteristics with the MSCs of the present invention. Once isolated, purified and culturally expanded, the mesenchymal stem cells of the present Application can be distinguished from the more complex cellular environment present in adherent cells of long-term bone marrow stromal culture as evidenced by Majumdar *et al*. and discussed above.

To overcome this deficiency in the rejection, the Examiner argues in the most recent Office Action (p. 4, lines 9-11) that "stromal cells used in the method of Nolta et al. for the transduction of human CD34 cells with retroviral vectors are mesenchymal stem cells that have been isolated, purified and culturally expanded from human mesoderm tissue". As discussed above, there is nothing in Nolta et al., Prockop and/or the '765 publication that suggests that these stromal cells

necessarily or inherently possess all of the properties of MSCs which have been isolated, purified and culturally expanded from human mesoderm tissue. The Examiner has put forth, at best, no more than the possibility that some unknown percentage of the heterogenous population of bone marrow stromal cells that were passaged 4 times for transduction of CD34 cells as taught by Nolta et al. are substantially identical to the MSCs (or necessarily or inherently possess all of the properties of MSCs) of present claim 5.

However, the Federal Circuit has stated that inherency may not be established in such manner, stating that: "If the prior art reference does not expressly set forth a particular element of the claim, that reference still may anticipate if that element is 'inherent' in its disclosure." *In re Robertson,* 169 F.3d 743, 745 (Fed. Cir. 1999). "Inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient." *Id.* (*quoting Continental Can Co. v. Monsanto Co.,*948 F 2d 1264, 1268 (Fed. Cir. 1991)) (internal quotation marks and citations omitted).

The Examiner must provide a basis in fact or technical reasoning to reasonably support the determination that the allegedly inherent characteristics necessarily flow from the teachings of the applied reference. *Ex Parte Levy*, 17 USPQ2d 1461, 1464 (Bd. Pat. App. & Inter. 1990). The Examiner has, however, failed to provide sufficient evidence in fact or technical literature to support this assertion. Absence such a showing that this characteristic necessarily flows from the stromal cells of Nolta et al, Nolta et al. cannot be relied on to teach the use of MSCs which have been isolated, purified and culturally expanded from human

mesoderm tissue in a method of transducing hematopoietic progenitor cells. Accordingly, the burden of establishing that the stromal cells of Nolta et al. necessarily or inherently possess the characteristics of the present claimed invention remains with the Examiner.

Therefore, Appellants respectfully submit that the present invention is patentable over Nolta *et al.* as evidenced by Prockop and/or the '765 publication because Nolta *et al.* fail do not teach all the limitations of claim 5. Accordingly, Appellants respectfully request that the 35 U.S.C. §102(b) rejection of claim 5 be withdrawn. Claims 3- 4 depend directly from claim 5, and therefore should be allowed because of the aforementioned deficiencies in the rejection with respect to claim 5 and because of the specific limitation recited in claims 3-4.

VII. ARGUMENTS FOR CLAIMS 2 and 4-5

Claims 2 and 4-5 were rejected under 35 U.S.C. §102(b) as being anticipated by Wells et al. as evidenced by Prockop and/or the '765 Publication.

The most recent Office Action, mailed November 16, 2010, argues that Wells *et al.* discloses a transduction method for human bone marrow CD34 progenitor cells from a Gaucher patient with retroviral vectors containing a normal human glucocerebrosidase cDNA, in the presence of an autologous bone marrow stromal support containing adherent stromal cells depleted of hematopoietic cells and macrophages that were obtained between passages 3 and 5. The Office Action further argues that the utilized bone marrow stromal support contains isolated mesenchymal stem cells or isolated multipotential bone marrow stromal cells as evidenced by the teachings of Prockop, including the disclosure that the adherent

cells used as feeder layers for hematopoietic stem cells have many of the characteristics of MSCs isolated by their adherence to plastic in the absence of non-adherent cells. The Office Action also argues that the terms "Mesenchymal stem cell" and "Marrow stromal cell" have been used interchangeably in the art as evidenced by the teaching of the '765 Publication. The Office Action concludes that the bone marrow stromal cells that were obtained between passages 3 and 5 for transduction as taught by Wells *et al.* are mesenchymal stem cells that have been isolated, purified and culturally expanded from human mesoderm tissue.

Applicants respectfully submit that claim 5 is not anticipated by Wells *et al.* as evidenced by Prockop and/or the '765 publication, because Wells *et al.* do not teach a homogenous population of mesenchymal stem cells that have been isolated, purified, and then culturally expanded, as claimed in the present application. Specifically, Applicants note that Wells et al. do not teach a homogenous population of human mesenchymal cells that have been isolated, purified, and then culturally expanded from human mesoderm tissue and the claimed isolated, purified and then culturally expanded homogenous population of mesenchymal stem cells are not an identical to the stromal cells taught by Wells *et al.*

In order for a claim to be anticipated each and every element of the claimed invention, operating in the same fashion to form the identical function as the claimed product must be literally present in a single prior art reference, arranged as in the claim. *Scripps Clinic & Research Found. v. Genentech, Inc.* 927 F.2d 1565, 1576 (Fed. Cir. 1991); Carella v. Starlight Archery & Pro Line Co., 804 F.2d at 138. "There must be no difference between the claimed invention and the referenced disclosure,

as viewed by a person of ordinary skill in the field of the invention." *Scripps Clinic & Research Found. v. Genentech, Inc., 927 F.2d at 1576; see also E.I. Du Pont de Nemours & Co. v. Polaroid Graphics Imaging. Inc.,* 706 F. Supp. 1135, 1142 (D. Del.1989), (aff'd, 887 F.2d 1095 (Fed. Cir. 1989) ("all of the same elements [must be] found in exactly the same situation and united in the same way ... in a single prior art reference") (quoting *Perkin Elmer Corp. v. Computervision, Corp.,* 732 *F.2d* 888, 894 *(Fed. Cir. 1984)).* It is not sufficient that each element be found somewhere in the reference, the elements must be "arranged as in the claim." *Lindemann Maschinenfabrik GmbH v. American Hoist & Derrick Co.,* 730 F.2d 1452, 1458 (Fed. Cir. 1984). Thus, any degree of physical difference between the patented product and the prior art, *no matter how slight,* defeats the claim of anticipation. *E.I. Du Pont de Nemours & Co. v. Polaroid Graphics Imaging, Inc.,* 706 F. Supp. at 1142.

Wells *et al*. teach:

> "To generate autolgous stromal monolayers, cryopreserved marrow from the patient with Gaucher disease was plated at a concentration of 5 x 10^5 cells/ml in tow types of media. The first medium was IMDM with 15% FCS, 15% HS, 10^{-4} M 2-mercaptoethanol, 10^{-6} M hydrocortisone, 50 U/ml penicillin G, 50 µg/ml streptomycin sulfate, and 2 mM L-glutamine. The second medium was IMDM with 10% FCS, 50 U/ml penicillin G, 50 µg/ml streptomycin sulfate, and 2 mM L-glutamine. All of the non-adherent cells were removed 24h after plating. Subconfluent layers of primary stromal cells were split by trypsinization. Stroma was used as a supporting layer for transduction between passages 3 and 5, after hematopoietic cells and macrophages had been depleted. Stromal cells were irradiated (20Gy) and plated at 5 x 10^5 cells per T-25 vent-cap flask in transduction medium the day before use." (p518, col. 2, 2^{nd} para).

Similar to the isolation technique of Nolta et al., the result of the isolation technique taught by Wells et al. is a heterogeneous, poorly defined population of marrow derived cells. There is nothing in Wells et al. that states that this population is a homologous population of mesenchymal stem cells, let alone a population of mesenchymal stem cells that have been isolated, purified, and then culturally expanded. The mere fact that Wells et al. teach that stromal cells have been passaged 3-5 times only suggests that an isolated heterogenous population has been isolated. There is nothing in Wells et al. that teaches this isolated population is homogenous and/or is subsequently culturally expanded.

In contrast, claim 5 recites a homogenous population of mesenchymal stem cells that have been isolated, purified, and then culturally expanded. The specification of the application which is used to construe this language teaches at p. 5, ll. 1-12 that:

> [m]esenchymal stem cells (MSCs) can be derived from marrow, periosteum, dermis and other tissues of mesodermal origin. The mesenchymal stem cells can be isolated and prepared according to methods known in the art, for example, a process for isolating, purifying, and expanding the marrow-derived mesenchymal stem cells in culture, i.e. in vitro, is described in U.S. Patent Nos. 5,197,985 and 5,226,914 and PCT Publication No. WO 92/22584 (1992) as well as numerous literature references by Caplan and Haynesworth. The stem cells may be isolated from other cells by density gradient fractionation, such as by Percoll gradient fractionation. The human mesenchymal stem cells also can include a cell surface epitope specifically bound by antibodies from hybridoma cell line SH2, deposited with the ATCC under accession number HB10743l antibodies form hybridoma cell line SH3, deposited with ATCC under accession number HB10744; or antibodies from hybridoma cell line SH4, deposited with the ATCC under accession number HB10745 (Emphasis added).

Appellants note that the mesenchymal stem cells taught in the present application are a specific cell type, possessing defined characteristics recognized by

those skilled in the art, as evidenced by Majumdar *et al.* (J. Cell. Phys. 178:57-66,1998). Majumdar *et al.* discuss the differences between isolated, purified mesenchymal stem cells (MSCs) and marrow-derived stromal cells (MDSCs) (see Abstract). Majumdar *et al.* teach that MSCs are morphologically distinct from MDSC cultures, and flow cytometric analyses show that MSCs are a homogeneous cell population (*Id.*; Figs. 1 & 2). In addition, MSCs were found to have greater steady state levels of cytokine expression than MDSCs (*See* Abstract and Fig. 3). Majumdar *et al.* disclose a method for isolating, purifying and culturally expanding MSCs that utilizes Percoll density centrifugation as a purification step (p58, first full para.). The use of Percoll purification is discussed in the present specification at p. 5, ll. 6-7 and p. 9, ll. 29-30.

Appellants further note that the present application differentiates between MSCs and Dexter stroma. Dexter stroma as discussed in the present specification is equivalent to the MDSCs discussed by Majumdar *et al.* (See Majumdar *et al.* p58, para. spanning col. 1-2 and Experimental Example p10, ll. 13-23). Thus, one skilled in the art at the time of the invention would have recognized that MSCs recited in claim 5 are a distinct cell population compared to the heterogeneous stromal cells of Wells *et al.*

In addition, while there are several art-recognized methods for arriving at a homogenous population of mesenchymal stem cells that have been isolated, purified, and culturally expanded, the present application provides examples of specific methods for arriving at a homogenous population of mesenchymal stem cells that have been isolated, purified, and culturally expanded. Conversely, the

present application does not provide examples of methods for arriving at the heterogeneous, poorly defined population of marrow derived cells of Wells et al.

The Examiner appears to assert (see Office Action, mailed November 16, 2010 at pg. 6, lines14-16) that because the claim language does not specify a method of isolation, purification, and culture expansion, the methods of Wells et al. are covered by the scope of claim 5. However, the Examiner must construe the claims in accordance with defined terms in the specification. While it is true that a specific method is not claimed, the specification does teach that MSCs are a distinct population from the more heterogeneous cell population of the marrow stroma (p. 5, ll. 14-17).

Wells et al. employ an isolation technique based on adherence of stromal cells to plastic cell culture plates. The only isolation and purification is the removal of non-adherent cells by washing the plates. Wells *et al.* do not characterize or demonstrate that the passaged adherent cells are a homogeneous population of mesenchymal stem cells or that there is even a high proportion of mesenchymal stem cells compared to other cell types. In fact, Wells *et al.* fails to discuss mesenchymal stem cells at all. Therefore, the isolated cell population taught by Wells et al. is not identical to the homogeneous cell population of mesenchymal stem cells that have been isolated, purified, and culture expanded as presently claimed.

Moreover, there is nothing in Wells et al. that teaches the passaged stromal cells of Wells et al. would inherently be a homogenous population of mesenchymal stem cells. The Examiner infers that mesenchymal stem cells of Wells et al. are isolated, purified, and expanded by referencing Prockop as support for the presence

of mesenchymal stem cells in the adherent cell population. However, Prockop does not support the argument that mesenchymal stem cells have been isolated, purified, and expanded. Contrary to the position taken by the Examiner, Prockop teaches that there are advantages to utilizing isolation and purification methods as opposed to the "crude procedure of Friedenstein," *i.e.,* the isolation of marrow stromal cells via adherence to plastic alone that is also used by Nolta *et al.* (see p72, col. 1, para. 3 and col. 2, para. 2). These advantages include that "the isolated cells are either clonal or nearly clonal, they express small amounts of bone cell markers such as alkaline phosphatase, and they can be induced in culture to express large amounts of the same markers…" (p72, col. 2, para 2).

In addition, the most recent Office Action argues that the terms "Mesenchymal stem cell" and "Marrow stromal cell" have been used interchangeably in the art as evidenced by the '765 Publication. Appellants fail to see the relevancy of this argument and respectfully submit that a person of skill in the relevant art would clearly recognize that a homogenous population of mesenchymal stem cells that have been isolated, purified, and then culturally expanded are distinct from the marrow stromal cells taught by Wells *et al.* Simply because the '765 Publication referred to a single cell type interchangeably as mesenchymal stem cells and marrow stromal cells, the '765 publication does not illustrate that the marrow stromal cells taught by Wells et al. are identical to the MSCs recited in claim 5.

As discussed above, Majumdar *et al.* discuss the differences between isolated, purified mesenchymal stem cells (MSCs) and marrow-derived stromal cells (MDSCs) (see Abstract). Majumdar *et al.* teach that MSCs are morphologically

distinct from MDSC cultures, and flow cytometric analyses show that MSCs are a homogeneous cell population (*Id.*; Figs. 1 & 2). In addition, MSCs were found to have greater steady state levels of cytokine expression than MDSCs (*See* Abstract and Fig. 3). Majumdar *et al.* disclose a method for isolating, purifying and culturally expanding MSCs that utilizes Percol density centrifugation as a purification step (p58, first full para.). The use of Percol purification is discussed in the present specification at p. 5, ll. 6-7 and p. 9, ll. 29-30.

Appellants note that the present application differentiates between MSCs and Dexter stroma. Appellants further note that Dexter stroma as discussed in the present specification is the same as the MDSCs discussed by Majumdar *et al.* (See Majumdar *et al.* p58, para. spanning col. 1-2 and Experimental Example p10, ll. 13-23.). Thus, one skilled in the art would recognize that the MSCs recited in claim 5 are a distinct cell population from the heterogeneous stromal cells discussed by Wells *et al.*

The most recent Office Action notes that the instant specification states "These results demonstrate that hMSCs are able to support ex vivo gene transfer into CD34 human hematopoietic progenitor cells that exhibit transduction efficiencies, cell expansion and drug resistance comparable to the levels produced in Dexter Stroma and FN enhanced transduction", and that "Dexter Stroma was derived from adhered bone marrow mononuclear cells that were passaged once". The statements cited by the Examiner were not intended to, nor do they illustrate that the cell populations of Dexter Stroma and the MSCs isolated from human mesoderm tissue are substantially identical cell populations. This statement was merely

included in the present Application to illustrate the effectiveness of the present invention in relation to other methods of *ex vivo* gene transfer into human hematopoietic progenitor cells known at the time of the present invention.

The Examiner argues in response to Appellants' previous argument put forth that the stromal cell population is devoid of most hematopoietic cells and contains MSCs as evidenced by Prockop (pg. 6, lines 17-21, of the most recent Office Action, mailed November 16, 2010) and that this bone marrow derived stromal cell population have many of the characteristics of MSCs (pg. 3, lines 20-22 of the most recent Office Action, mailed November 16, 2010).

However, a heterogeneous bone marrow stromal cell population is not equivalent to a homogenous population of mesenchymal stem cells isolated, purified and then culturally expanded from human mesoderm tissue even if it shares many characteristics with MSCs of the present invention. Once isolated, purified and culturally expanded, the mesenchymal stem cells of the present Application can be distinguished from the more complex cellular environment present in adherent cells of long-term bone marrow stromal culture as evidenced by Majumdar *et al*. and discussed above.

To overcome this deficiency in the rejection, the Examiner argues in the most recent Office Action (p. 4, lines 9-11) that "stromal cells used in the method of Wells et al. for the transduction of human CD34 cells with retroviral vectors are mesenchymal stem cells that have been isolated, purified and culturally expanded from human mesoderm tissue". As discussed above, there is nothing in Wells et al., Prockop and/or the '765 publication that suggests that these stromal cells

necessarily or inherently possess all of the properties of MSCs which have been isolated, purified and culturally expanded from human mesoderm tissue. The Examiner has put forth, at best, no more than the possibility that some unknown percentage of the heterogeneous population of bone marrow stromal cells that were passaged 4 times for transduction of CD34 cells as taught by Wells et al. are substantially identical to the MSCs (or necessarily or inherently possess all of the properties of MSCs) of present claim 5.

However, the Federal Circuit has stated that inherency may not be established in such manner, stating that: "If the prior art reference does not expressly set forth a particular element of the claim, that reference still may anticipate if that element is 'inherent' in its disclosure." *In re Robertson,* 169 F.3d 743, 745 (Fed. Cir. 1999). "Inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient." *Id.* (*quoting Continental Can Co. v. Monsanto Co.,*948 F 2d 1264, 1268 (Fed. Cir. 1991)) (internal quotation marks and citations omitted).

The Examiner must provide a basis in fact or technical reasoning to reasonably support the determination that the allegedly inherent characteristics necessarily flow from the teachings of the applied reference. *Ex Parte Levy*, 17 USPQ2d 1461, 1464 (Bd. Pat. App. & Inter. 1990). The Examiner has, however, failed to provide sufficient evidence in fact or technical literature to support this assertion. Absence such a showing that this characteristic necessarily flows from the stromal cells of Wells et al, Wells et al. cannot be relied on to teach the use of MSCs which have been isolated, purified and culturally expanded from human

mesoderm tissue in a method of transducing hematopoietic progenitor cells. Accordingly, the burden of establishing that the stromal cells of Wells et al. necessarily or inherently possess the characteristics of the present claimed invention remains with the Examiner.

Therefore, Appellants respectfully submit that the present invention is patentable over Wells *et al.* as evidenced by Prockop and/or the '765 publication because Wells *et al.* fail do not teach all the limitations of claim 5. Accordingly, Appellants respectfully request that the 35 U.S.C. §102(b) rejection of claim 5 be withdrawn. Claims 2 and 4 depend directly from claim 5, and therefore should be allowed because of the aforementioned deficiencies in the rejection with respect to claim 5 and because of the specific limitations recited in claims 2 and 4.

VII. ARGUMENTS FOR CLAIMS 5 and 7

Claims 5 and 7 were rejected under 35 USC 103(a) as being unpatentable over either Nolta et al. or Wells et al. in view of Prockop and Caplan et el.

The most recent Office Action, mailed November 16, 2010, argues that Nolta et al. disclose a transduction method for human CD34 cells isolated from bone marrow and peripheral blood with retroviral vectors containing either the bacterial neo gene, or normal human glucocerebrosidase in the presence of stroma generated by 4th passaged human allogeneic bone marrow stromal cells prior to the plating of CD34 cells. The Office Action also argues that the utilized bone marrow stromal cell population derived from bone marrow spicules is devoid of most hematopoietic cells except for mature macrophages which comprised less than 1% of the culture and that Nolta et al. teach the isolation of transduced, nonadherent CD34 cells after the

transduction by vigorous flushing and plating the collected cells twice to eliminate adherent cells.

The Office Action argues that Wells et al. disclose a transduction method for human bone marrow CD34 progenitor cells from a Gaucher patient with retroviral vectors containing a normal human glucocerebrosidase cDNA, in the presence of an autologous bone marrow stromal support containing adherent stromal cells depleted of hematopoietic cells and macrophages that were obtained between passages 3 and 5. The Office Action further argues that Wells et al. teach the isolation of transduced, nonadherent CD34 cells after the transduction.

The Office Action argues that prior to the filing date of the present application, Prockop taught that bone marrow stromal cells (MSC) can be isolated from other cells in marrow by their tendency to adhere to tissue culture plastic; and that the cells have many of the characteristics of stem cells form tissues that can roughly be defined as mesenchymal because they can be differentiated into osteoblasts, chondrocytes, adipocytes, and myoblasts. The Office Action also argues that Prockop discloses that experiments on the differentiation of MSCs have been carried out with cultures described by the pioneering work of Friedenstein as well as by other groups that have attempted to prepare more homogneous populations.

The Office Action argues that Caplan et al. also taught a method of isolating, purifying and culturing expanding human mesenchymal stem cells (hMSCs) from bone marrow, including a cell population having greater than 95% of hMSCs that express SH2, SH3 and SH4 antigens. The Office Action also argues that Caplan et al. teach monoclonal hybridoma cell lines that synthesize and secrete monoclonal

antibodies specific from hMSCs' SH2, SH3 and SH4 surface antigens; and that these monoclonal antibodies can also be used in the isolation of mesenchymal stem cells through various means.

The Office Action concludes that it would have been obvious for an ordinary skilled artisan to modify the teachings of either Nolta et al. or Wells et al. by also using at least a homogenous population of human bone marrow derived MSCs expressing uniformly SH2, SH3 and SH4 surface antigens, that has been isolated, purified and culturally expanded to support and/or increase gene transduction for human HSCs in light of Prockop and Caplan et al. because:

> "an ordinary skilled artisan would have been motivated to carry out the above modification because Prockop already taught that adherent cells used as feeder layers for HSCs have many of the characteristics of bone marrow stromal cells that are characterized by their tendency to adhere to tissue culture plastic and are capable of differentiating into osteoblasts, chondrocytes, adipocytes, and even myoblasts. Moreover, an isolating and purifying method for a homogenous population of human bone marrow mesenchymal cells expressing uniformly SH2, SH3, and SH4 surface antigens was also taught by Caplan et al."

Appellants respectfully submit that claim 5 is patentable over either Nolta et al. or Wells et al. in view of Prockop and Caplan et el. because: (1) the Office Action has failed to provide a reasonable rationale to combine either Nolta et al. or Wells et al. with Prockop and Caplan et el. to teach transforming human hematopoietic progenitor cells in the presence of the isolated, purified, and culturally expanded human mesenchymal stem cells; and (2) one of ordinary skill in art would not find it predictable and/or have a reasonable expectation of success in view of either Nolta et al. or Wells et al. and Prockop and Caplan et el. to transform human

hematopoietic progenitor cells in the presence of the isolated, purified, and culturally expanded human mesenchymal stem cells.

i. The Office Action has failed to provide a reasonable rationale to combine either Nolta et al. or Wells et al. with Prockop and Caplan et el. to teach transforming human hematopoietic progenitor cells in the presence of the isolated, purified, and culturally expanded human mesenchymal stem cells.

As discussed above, to overcome the deficiencies in the teachings of Nolta et al. or Wells et al. as to the use of a homogenous population of mesenchymal stem cells for co-culturing human hematopoietic cells that are transformed, the Office Action concludes:

> "an ordinary skilled artisan would have been motivated to carry out the above modification because Prockop already taught that adherent cells used as feeder layers for HSCs have many of the characteristics of bone marrow stromal cells that are characterized by their tendency to adhere to tissue culture plastic and are capable of differentiating into osteoblasts, chondrocytes, adipocytes, and even myoblasts. Moreover, an isolating and purifying method for a homogenous population of human bone marrow mesenchymal cells expressing uniformly SH2, SH3, and SH4 surface antigens was also taught by Caplan et al.

Appellants fail to see the relevance of this statement as to why one skilled in the art would use a homogenous population of mesenchymal stem cells for co-culturing human hematopoietic cells that are transformed. This statement merely notes two facts: (1) Prockop taught "adherent cells used as feeder layers for HSCs have many of the characteristics of bone marrow stromal cells that are characterized by their tendency to adhere to tissue culture plastic and are capable of differentiating into osteoblasts, chondrocytes, adipocytes, and even myoblasts"; and (2) that Caplan et al. taught "isolating and purifying method for a homogenous population of human bone marrow mesenchymal cells expressing uniformly SH2, SH3, and SH4

surface antigen". This statement however does not provide a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does.

The Supreme Court of the United States acknowledged that rejections on obviousness grounds cannot be sustained by mere conclusory statements, and that instead, there must be some rational underpinning to support the legal conclusion of obviousness. *KSR Int'l Co. v. Teleflex*, 82 USPQ2d 1385, 1396 (2007). In particular, to establish a *prima facie* case for obviousness, there must be "a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does." *Takeda Chemical Indus., Ltd. v. Alphapharm Pty. Ltd.,* 492 F.3d 1350, 1356-57 (Fed. Cir. 2007) *quoting KSR Int'l Co. v. Teleflex*, 82 USPQ2d 1385, 1396 (2007).

Here, the Examiner has merely noted two facts in Prockop and Caplan et al. and has failed to provide a reasonable rationale as to "why" a skilled artisan would combine these teachings with the teachings of Nolta et al. or Wells et al. to co-culture human hematopoietic progenitor cells with a homogenous population of human mesenchymal stem cells that have been isolated, purified and then culturally expanded from human mesoderm tissue.

Moreover, it has been held that a claimed composition would have not have been obvious where there was no reason to modify the closest prior art composition to obtain the claimed composition and the prior art taught that modifying the closest prior art would destroy its advantageous properties. *Eisai Co. Ltd. V. Dr. Reddy's Labs., Ltd.*, 533 F.3d 1353 (Fed Cir. 2008).

Here, Nolta et al. and Wells et al., which was identified by the Examiner as the closest prior art, teach methods for transducing CD34 in the presence of stroma generated by passaging and isolating human bone marrow stromal cells that adhere to plastic. As discussed above, the prior art cited by the Office Action provides no teaching that a homogenous population of human mesenchymal stem cells that have been isolated, purified and then culturally expanded from human mesoderm tissue would be desirable to use compared to other isolated cell populations derived from bone marrow. Thus, the Examiner has not identified any reason which would have prompted the ordinary artisan to select a population of isolated, purified, and culturally expanded human mesenchymal stem cells. Accordingly, the Office Action has failed to provide a reasonable rationale as to why a skilled artisan would transform human hematopoietic progenitor cells with a polynucleotide comprising exogenous genetic material encoding a protein in the presence of the isolated, purified, and culturally expanded human mesenchymal stem cells.

ii. <u>One of ordinary skill in art would not find it predictable and/or have a reasonable expectation of success of transforming hematopoietic progenitor cells to express a protein by co-culturing human hematopoietic progenitor cells with a homogenous population of human mesenchymal stem cells that have been isolated, purified and then culturally expanded from human mesoderm tissue.</u>

In *KSR*, the Supreme Court stated that when an obvious modification "leads to the anticipated success," the invention is likely the product of ordinary skill and is obvious under 35 U*.S.C.* § *103,* 127 S. *Ct. at 1742.* "[O]bviousness cannot be avoided simply by a showing of some degree of unpredictability in the art so long as there was a reasonable probability of success." *Pfizer, 480 F.3d at 1364* (citing *In re Corkill,* 771 *F2d 1496, 1500 (Fed. Cir. 1*985)).

Cases following *KSR,* however, have found that obviousness is not found where the prior art [gives] either no indication of which parameters [are] critical or no direction as to which of many possible choices is likely to be successful" *In re O'Farrell, 853 F.2d* 894, *903 (Fed. Cir*. 1988). In such cases, "courts should not succumb to hindsight claims of obviousness. "*In re Kubin,* 561 *F.3d 1351, 1359 (Fed Cir. 2009).* Similarly, patents are not barred just because it was obvious "to explore a new technology or general approach that seemed to be a promising field of experimentation, where the prior art gave only general guidance as to the particular form of the claimed invention or how to achieve it." *In re O'Farrell, 853 F.2d at 903.*

As discussed above, Nolta et al. and Wells et al. merely teach methods for transduction of hematopoietic stem cells on stromal feeder cells and do not specifically teach the use of a homogenous population of human mesenchymal stem cells that have been isolated, purified and then culturally expanded from human mesoderm tissue.

As discussed in the most recent Office Action, Prockop teaches that several groups of investigators had attempted to prepare more homogeneous populations of the marrow stromal cells of Friedenstein. However, a caveat to this teaching is that none of the protocols had been used in more than one laboratory, and it had not been shown whether they isolate the same cells. Furthermore, it had not been demonstrated that the cells retain all the multipotential properties of the marrow stromal cells isolated by Friedenstein's protocol. (Prockop, page 72, col. 2, ¶2). Thus, Prockop teaches that at the time of the filing of the present application it was unknown which "more homogenous" populations of isolated marrow stromal cells

retained any of the characteristics of the crude heterogeneous populations described by Friedenstein.

In addition, Prockop does not teach and the Examiner has not presented evidence that any of these potential isolated cell types are the MSCs of the present invention, nor has the Examiner presented any evidence that a skilled artisan would predict successful transduction using the more homogenous populations of marrow stem cells. The fact that more homogenous populations of marrow stromal cells can be isolated and potentially used in methods for transducing hematopoietic progenitor cells does not show that such populations of isolated marrow stromal cells will be successful in methods of transducing hematopoietic progenitor cells.

Moreover, one of ordinary skill in the relevant art would not have found it predictable and/or had a reasonable expectation of success that human mesenchymal stem cells that have been isolated, purified and then culturally expanded from human mesoderm tissue would be effective in a method for transforming hematopoietic progenitor cells to express a protein.

Caplan et al. as discussed above teach a method of isolating, purifying and culturing expanding human mesenchymal stem cells (hMSCs) from bone marrow, including a cell population having greater than 95% of hMSCs that express SH2, SH3 and SH4 antigens. Caplan et al. does not teach that the human mesenchymal stem cells would be effective in a method for transforming hematopoietic progenitor cells to express a protein. Furthermore, the Examiner has not presented any evidence that the MSCs of the present invention had an established function in HSC transduction at the time of invention that would suggest the success of the presently

claimed invention. Therefore, the solution found in the present invention and recited in claim 5, namely the use of a homogenous population of human mesenchymal stem cells that have been isolated, purified and then culturally expanded from human mesoderm tissue in a method for transforming hematopoietic progenitor cells to express a protein is not "predictable" as required for a determination of obviousness.

Thus, at the time of filing the present application, it was not known that the MSCs of the present invention (*i.e.,* isolated, purified, and culturally expanded human mesenchymal stem cells) had an established function in HSC transduction. Therefore, one skilled in the art could not infer, find it predictable, and/or have a reasonable expectation of success that the MSC populations recited in claim 5 would be effective in a method for transforming hematopoietic progenitor cells to express a protein. It has been held that a claim is not obvious where the improvement of the prior art is more than a predictable use of prior art elements according to their known function or use. *In re Kubin,* 561 F.3d 1351, 1359 (Fed Cir. 2009). Therefore, claim 5 is not obvious in view of Nolta et al., Wells et al., Prockop and Caplan et al.

In regards to claim 7, the Examiner concedes that neither Nolta et al. nor Wells et al. teach specifically, the homogenous population of mesenchymal stem cells uniformly expressing SH2, SH3, and SH4 antigens and lacking surface markers for T and B lymphocytes, macrophages, and endothelial cells.

Prockop teach that crude heterogenous bone marrow stromal cells (MSC) populations can be isolated, as described by Friedenstein, from other cells in marrow by their tendency to adhere to tissue culture plastic; and that the cells have many of the characteristics of stem cells. Prockop also taught that several groups of

investigators had attempted to prepare more homogeneous populations of these marrow stromal cells but that it was unknown which populations of isolated marrow stromal cells retained any of the characteristics of the populations described by Friedenstein and used in Nolta et al. and Wells et al.

Caplan et al. teach: isolating, purifying and culturing expanding human mesenchymal stem cells (hMSCs) from bone marrow, including a cell population having greater than 95% of hMSCs that express SH2, SH3 and SH4 antigens; that monoclonal hybridoma cell lines that synthesize and secrete monoclonal antibodies specific from hMSCs' SH2, SH3 and SH4 surface antigens; and that these monoclonal antibodies can also be used in the isolation of mesenchymal stem cells through various means. However, Caplan et al. do not teach or give any indication that these cell populations would be effective in a method for transforming hematopoietic progenitor cells to express a protein.

Therefore claim 7 should be allowed because of the aforementioned deficiencies in the rejection with respect to claim 5 and because of the specific limitations recited in claims 7.

Conclusion

In view of the foregoing remarks, Appellants submit that the rejection of claims 1 and 8-10 under 35 U.S.C. §103(a) is improper. Appellants respectfully request that the final rejection of the claims be withdrawn and the subject application be passed to issue.

Please charge any deficiency or credit any overpayment in the fees for this Appeal Brief to Deposit Account No. 20-0090.

Respectfully submitted,

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VIII. CLAIMS APPENDIX

Claim 1 (Cancelled)

Claim 2 (Finally Rejected): The method of claim 5, wherein the mesenchymal stem cells are autologous to the hematopoietic progenitor cells.

Claim 3 (Finally Rejected): The method of claim 5, wherein the mesenchymal stem cells are allogeneic to the hematopoietic progenitor cells.

Claim 4 (Finally Rejected): The method of claim 5 further comprising separating the transformed human progenitor cells from the mesenchymal stem cells.

Claim 5 (Finally Rejected): A method for transforming hematopoietic progenitor cells to express a protein, comprising co-culturing human hematopoietic progenitor cells with a homogenous population of human mesenchymal stem cells that have been isolated, purified and then culturally expanded from human mesoderm tissue, and transforming the human hematopoietic progenitor cells with a polynucleotide comprising exogenous genetic material encoding a protein in the presence of the isolated, purified, and culturally expanded human mesenchymal stem cells, wherein said protein is expressed.

Claim 6 (Cancelled):

Claim 7 (Currently Amended/Finally Rejected): The method of claim 5, the homogenous population of mesenchymal stem cells uniformly expressing SH2, SH3, and SH4 surface antigens, and lacking surface markers for T and B lymphocytes, macrophages, and endothelial cells.

IX. EVIDENCE APPENDIX

Majumdar, M.K., Thiede, M.A., Mosca, J.D., Moorman, M. & Gerson, S.L. (1998) Phenotypic and functional comparison of cultures of marrow-derived mesenchymal stem cells (MPCs) and stromal cells. *Journal of Cellular Physiology*, 176, 57 – 66.

X. RELATED PROCEEDING APPENDIX

There are no related appeals, interferences, or judicial procedures under 37 C.F.R. §41.37(1)(c)(ii).